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EXAMINER	
JONES, DAMERON LEVEST	

ART UNIT	PAPER NUMBER
1616	15

DATE MAILED: 10/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 10/014,335	Applicant(s) FRITZBERG ET AL.	
	Examin r D. L. Jones	Art Unit 1616	

-- The MAILING DATE of this c mmunication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/18/03; 8/4/03; and 9/12/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-93 and 100-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *86-93* is/are allowed.

6)☒ Claim(s) *100 and 103-105* is/are rejected.

7)☒ Claim(s) *101 and 102* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11&13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS, Paper No. 14* .

ACKNOWLEDGMENTS

1. The Examiner acknowledges receipt of Paper No. 12, filed 6/18/03, wherein claims 86 and 93 were amended and claims 94-99 were canceled.

Note: Claims 86-93 and 100-105 are pending.

RESPONSE TO APPLICANT'S AMENDMENT/ARGUMENTS

2. The Applicant's arguments filed 6/18/03 (Paper No. 12) to the rejection of claims 86-105 made by the Examiner under 35 USC 103, 112, and/or 101 have been fully considered and deemed persuasive for reasons of record in Applicant's response. Therefore, all outstanding rejections are hereby withdrawn.

NEW GROUNDS OF REJECTION

103 Rejection

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 100 and 103-105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simon et al (US Patent No. 5,762,907).

Simon et al disclose radiopharmaceutical compositions comprising at least one radionuclide complexed with a ligand (see entire document, especially, abstract). In

addition, Simon et al disclose (1) concern when administering any radiopharmaceutical is the potential for radiolytic degradation of the organic molecules present in the formulation which may in turn alter the biodistribution of the radioisotope or result in toxic byproducts. There is also concern when high amounts of radioactivity is needed. Hence, one approach in order to prevent radiolysis is the addition of a free radical inhibitor (column 1, lines 53-64). (2) Simon et al generated an 'improved' composition comprising a radionuclide (e.g., 166Ho) which is complexed with a ligand (e.g., DOTMP) that may contain a divalent metal ion that does not interfere with the radiopharmaceutical complex (column 2, lines 35-68). (3) Ca2+ is the preferred divalent metal. The radiopharmaceutical compositions are prepared such that about 0.25 to about 5 moles of the divalent metal is present per mole of ligand. More preferred is a ratio of about 0.5 to about 3 moles (column 3, lines 12-26). (4) Another way to prepare the divalent metal radiopharmaceutical composition is to add the divalent metal as its chloride or hydroxide to the ligand and then adjust the pH (column 3, lines 30-51). (5) Simon et al disclose that, for example, 153Sm-EDTMP complexes using their method of preparing the radiopharmaceutical, reduces radiolysis of the ligand without altering the performance of the radiopharmaceutical (column 4, lines 28-36). (6) In column 6, Table 1 and lines 52-68, a table of the inhibition of radiolytic degradation is disclosed. Various samples were analyzed over various time periods. (7) In Example 3, columns 7-8, various ratios of Ca2+ were added to samples. (8) In Example 4, Ca2+ was utilized and the pH was adjusted above 6 when Ca(OH)2 and EDMTP were used. While Simon et al disclose the use of a radioprotectant for inhibiting radiolysis, the reference does not

specifically disclose 166Ho-DOTMP with the radioprotectant, but does disclose other radionuclide-ligand combinations.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to generate a composition comprising 166Ho complexed with DOTMP and an effective antiradiolytic amount of a pharmaceutically acceptable radioprotectant because Simon et al disclose a composition comprising at least one radionuclide complexed with a ligand that may have a radioprotectant present. Possible radionuclides include 166Ho and possible ligands include DOTMP. Also, Simon et al disclose that the addition of a radioprotectant in combination with the radiopharmaceutical is known in the art since whenever an radiopharmaceutical is administered to a subject, there is a potential for radiolytic degradation of the organic molecule (e.g. DOTMP) which may alter the biodistribution of the radioisotope or result in toxic byproducts. Hence the addition of a divalent metal ion such as Ca2+ was used (column 1, lines 53-62; columns 2-3, bridging paragraph; column 3, lines 12-61). Also, it would have been obvious to a skilled practitioner that the composition be stable for at least 72 hours under ambient conditions because column 6, Table I and lines 54-56 indicate that at 70.5 hours the percent radiometric degradation of Sample III was only 0.1%. Hence, the skilled practitioner would not expect that an additional hour would drastically reduce the stability of a composition that has been stable for approximately 71 hours. In addition, a skilled practitioner in the art would recognize, from the examples of Simon et al, that it is common to adjust the pH to a desired number. For example, in Example 4, column 8, lines 43-45, in the preferred method of preparing the

Ca-kit, Ca(OH)2 and ligand were combined in a beaker, water was added, the mixture was stirred, and the pH was adjusted above 6.

CLAIM OBJECTIONS

5. Claims 101 and 102 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Note: The claims are distinguished over the prior art in combination with all the limitations of their respective intervening claims because the prior art neither anticipates nor renders obvious a composition comprising 166Ho complexed with DOTMP and an effective radiolytic amount of a pharmaceutically acceptable radioprotectant.

ALLOWABLE CLAIMS

6. Claims 86-93 are allowable over the prior art of record. The claims are distinguished over the prior art of record because the prior art neither anticipates nor renders obvious a therapeutic method of treating bone associated cancer having the steps as set forth in independent claim 86. Specifically, the claims are distinguished over the prior art because a method of such wherein 166Ho-DOTMP in combination with an antiradiolytic amount of a radioprotectant and later melphalan as set forth in independent claim 86 is not anticipated or obvious.

COMMENTS/NOTES

7. Applicant is respectfully requested to submit copies of the claims for application numbers: 10/159,245; 10/172,363; and 10/601,081 which Applicant suggested that the Examiner review in Paper No. 14, filed 9/12/03. Copies of the claims are being requested because at the time of examination, the cases were not available for the Examiner to review.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Mon.-Fri., 6:45 a.m. - 3:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (703) 308 - 2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

D. L. Jones
Primary Examiner
Art Unit 1616

October 7, 2003